



Activity 5

Making Hard Decisions

Focus: Students explore several resources to evaluate proposals to combat AIDS, VRSA, and measles and recommend one proposal to support.

At a Glance

Major Concepts: Infectious diseases have a devastating impact nationally and globally, but a variety of strategies can alleviate suffering due to these diseases. Because resources are limited, allocating funds among projects that address different diseases raises complex ethical questions. Understanding the relevant biological principles can help in making these difficult decisions.

Objectives: After completing this activity, students will

- understand that proposals to combat infectious diseases can be evaluated using several criteria,
- be able to provide a rationale for accepting or rejecting proposals based on the magnitude of the situation and their likely effectiveness,
- understand that different people will define and weigh criteria differently as they evaluate questions about allocating funds for specific purposes, and
- understand that it is possible for people to hold quite different positions on a controversial topic and still participate in a reasoned discussion about it.

Prerequisite Knowledge: Students should be familiar with problems in controlling infectious diseases, such as the evolution of drug resistance and the challenge of administering vaccines to a significant proportion of the population.

Basic Science-Public Health Connection: Basic research has led to effective treatments and preventive measures to control infectious diseases. In this activity students see that implementing these measures is challenging, both financially and logistically, and requires that difficult decisions be made.

Implementation also brings us full circle: The problems we discover as we attempt to control infectious diseases are new problems for research to address.

The continuing—and growing—problem of infectious diseases in the world requires that money be spent to better understand the factors involved in infectious diseases and their spread, to alleviate suffering, and to prevent disease where possible. Much of the money spent in the United States to fight infectious diseases is federal money, allocated through well-established and closely monitored agencies and programs. Some of the money, however, is private money—money that is made available through the beneficence of private foundations and individual donors.

Whether the money is public or private, someone, somewhere, has to decide how to allocate it: to whom it will be given and why, and how it will be spent and where and when. These decisions are not easy. Frequently, they are made

Introduction

by carefully considering many competing requests for funds, and the decisions reflect the degree to which, in the minds of the reviewers, the requests meet the funding criteria that have been established for use of the money.

In this activity, students consider three proposals for spending \$5 million that a private foundation has made available to combat infectious diseases. Each proposal addresses a different infectious disease (AIDS; measles; and vancomycin-resistant *Staphylococcus aureus*, or VRSA) and proposes different actions. Students use three reference databases to learn about each disease and evaluate the proposals on the basis of two criteria: magnitude (how important it is that the situation described in the proposal be addressed now) and effectiveness (how likely it is that the proposed project will address the situation successfully). Finally, students recommend which proposal to fund, provide reasons for their recommendations, and discuss differences in their evaluations as a way to understand how complex such decisions can be.

Materials and Preparation

You will need to prepare the following materials before conducting this activity:

- Master 5.1, *The Proposals* (make 1 copy per student)
- Master 5.2, *Reference Database—AIDS* (make 1 copy per team)
- Master 5.3, *Reference Database—Measles* (make 1 copy per team)
- Master 5.4, *Reference Database—VRSA* (make 1 copy per team)
- Master 5.5, *Proposal Criteria Matrix* (make 1 copy per student)
- Master 5.6, *Proposal Summary Matrix* (make 1 copy per student)
- Master 5.7, *Reflection Questions* (make 1 transparency)

Procedure



This is an opportunity for students to review what they learned in the previous activities and for you to assess their understanding informally. For a more formal assessment of student understanding, ask students to write individual responses to the questions.

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- 1. Introduce the activity by saying something like, “We’ve been studying infectious diseases and the reasons why ‘new’ diseases are emerging and ‘old’ ones are re-emerging. What are some of those reasons? What steps can we take to avoid disease emergence and re-emergence? How can research contribute to better ways to control infectious diseases?”**

Reasons for disease emergence and re-emergence developed in the previous activities include environmental changes, indiscriminate use of antibiotics, and failure to vaccinate populations. Steps that can be taken to avoid disease emergence and re-emergence include carefully considering the impact of development in wilderness areas and being alert to the possibility of pathogens having access to a new and/or larger host population, avoiding unnecessary uses of antibiotics, and increasing efforts to enforce vaccination. Research can help us develop better ways to recognize and understand new pathogens, create new or improved antimicrobial drugs to prevent or treat infection, develop new vaccines to protect individuals and the population, and discover new ways to prevent transmission of infection.

- 2. Continue the discussion by saying something like, “Fighting infectious diseases requires money as well as knowledge. There is a limit, however, to the money that is available for this purpose. How do people decide where to invest money in fighting infectious diseases?” Entertain some answers, then explain that in this activity, students will consider proposals to fight three different diseases, investigate each of these diseases, and recommend one proposal to fund. Indicate that their recommendations will be based on two criteria, “magnitude” and “effectiveness,” which will be described in the activity. Their recommendations also must include reasons for funding one proposal but not the other two.**

In the first script segment (see Step 3), the representative of the funding agency explains that students’ recommendations are to be based on the criteria of magnitude and effectiveness, and gives examples of the questions that students must answer to determine the magnitude of each situation and how effective the proposed plan is likely to be. Those and additional questions related to magnitude and effectiveness also appear on Master 5.5, *Proposal Criteria Matrix*.

You may want to indicate to students that there are valid reasons for recommending each proposal. Explain that this activity is like “real life” in that we frequently have to make difficult choices among several “good” options (or among several “bad” options).

Magnitude of the problem and effectiveness of the proposed approach are two criteria that are typically applied in making decisions about a plan to address a societal problem. With regard to infectious disease, magnitude refers to the current burden of illness, as well as the potential for this burden to increase in the future. Effectiveness refers to how well the proposal will alleviate the serious consequences of the disease.

A third criterion—means—often is used to make decisions about plans to address societal problems. Means refers to how well we can accomplish the actions described in the plan. For example, proposing that we spend money to distribute a “cure” for AIDS is not realistic because no cure is available at this time. In this activity, students consider means as part of their evaluation of the second criterion, effectiveness. That is, if a team judges a proposed project to have high “effectiveness,” the team believes there are means available to accomplish it.

Most funding agencies have an established review process and evaluation criteria for proposals submitted to them. NIH uses a peer review system, that is, external scientists familiar with the health issues, techniques, and research models in the proposals review and make recommendations about the scientific merit of the proposals. NIH specifies five major criteria for evaluation of proposals: significance (similar to the criterion of “magnitude” in the activity), approach (similar to “effectiveness”), innovation, experience of the principal investigator(s), and institutional support for the project.



Basic research has contributed to the public health management of all three of these diseases. Research on the measles virus in the 1950s and 1960s led to the development of a vaccine to prevent the disease. Research into HIV replication revealed vulnerable points in its infectious cycle, leading to the proteases now used to increase both the quality and the length of life for those who are HIV-positive. Research demonstrating that antimicrobial resistance genes can be passed from one bacterial species to another alerted health officials to the need for increased surveillance for resistant pathogens and reinforced the need to use antimicrobials prudently and to conduct research to develop new, more effective drugs.

3. Distribute one copy of Master 5.1, *The Proposals*, to each student. Also distribute one copy each of Masters 5.2, 5.3, and 5.4, *Reference Databases*, to each team. Organize students into their teams and direct them to read *The Proposals*, then proceed directly into their research using the information provided in the reference databases. Tell the teams that they have 30 minutes to complete their work.

4. Distribute Master 5.5, *Proposal Criteria Matrix*, and Master 5.6, *Proposal Summary Matrix*, as students begin their work and tell them that at the end of the 30 minutes, each team should be prepared to announce its recommendation and explain its rationale to the class.

While the student teams are conducting their research, move among them to make sure they understand each situation and the questions they are to answer. For example, ask them what each group of applicants proposes to do (AIDS applicants: produce and distribute drugs to HIV-positive individuals; measles applicants: produce and distribute vaccine to susceptible people around the world; VRSA applicants: develop new drug therapies against *Staphylococcus aureus*).

5. Ask each team to identify a spokesperson to tell the class which proposal the team recommends and the reason it selected that proposal. As the teams report their decisions, tally the number recommending each proposal.

6. Invite students to look at the results of the tally and ask them if they can explain the differences, considering that each team worked with the same information.

Students may respond with comments such as “We thought that, even if the plan had problems, AIDS is so terrible that we should support any plan that could possibly help” or “We thought that the measles plan had a pretty sure chance of working, whereas the others weren’t as likely to be effective.” Encourage this kind of discussion and point out that some teams gave more weight to the “magnitude” criterion and others gave more weight to the “effectiveness” criterion.

If all teams recommended the same proposal, tell them that other evaluators may well have recommended different proposals. Give them some possible rationales for those recommendations and ask them what explanation they can give for the different choices.

7. Display a transparency made from Master 5.7, *Reflection Questions*, and ask each team to work together to list as many responses to each question as they can. Conclude the activity by asking each team to give one of its answers and list it on the transparency.

Question 1 How did understanding the biology of infectious diseases help you make your decision?

Students may indicate that understanding how natural selection leads to the evolution of antibiotic-resistant bacteria helped them evaluate the likelihood of the emergence of VRSA, or that understanding herd immunity helped them assess the effectiveness of a vaccination program to eliminate measles.

Question 2 What else did you consider in making your decisions?

Students may say that they felt it was important to consider the number of people affected by the disease, or the impact the disease would have on the families of the victims (for example, “AIDS orphans”) or on the countries where the victims live (for example, the loss of productivity due to illness and death of AIDS victims in their prime working years).



Step 7 addresses the activity’s major concept. Students should understand that making policy decisions about spending money to combat infectious diseases is complex and there is typically no one “right” decision. Students also should recognize that understanding the biology underlying such diseases can help inform the decisions that ultimately are made.

The Proposals

Characters

Foundation Officer

AIDS Treatment Administrator

Public Health Physician

Hospital Administrator

Segment 1: Introducing the Proposals

Foundation Office

FOUNDATION OFFICER: Our organization funds research projects that are focused on relieving human suffering from disease. This year we have \$5 million to award for a single project. I've narrowed the field down to three strong proposals for work on three very different diseases. Believe me, these are tough decisions. We'd like you to consider two major criteria in making your recommendation. First, evaluate the magnitude of the situation. For example, how many people are affected by the disease? How serious are the consequences of the disease for the individual and for society?

Second, we need to know how effective the proposed plan will be for fighting or preventing the disease. Will we be able to get the treatments to those who are affected by the disease? If the plan is to develop a new treatment or prevention strategy, how likely is it to be successful? Rate these proposals using these two criteria and then give me a final recommendation.

Segment 2: Proposal 1

AIDS Clinic

AIDS TREATMENT ADMINISTRATOR: AIDS is now a worldwide epidemic that affects every sector of society. The most effective way to deal with AIDS is with powerful drugs. We attack the disease with drugs like AZT. It stops the virus from replicating and keeps the amount of virus in the blood low. By doing that and treating the symptoms at the same time, the patient will survive 5, 10 years, even more. Hopefully, then maybe the body takes over, and holds off the disease on its own. It isn't a cure. But living with the disease is better than dying with it. The problem is that these drugs are expensive. Our proposal is simple. Give us the money and we will give years of life to our patients.

Segment 3: Proposal 2

Physician's Office

PUBLIC HEALTH PHYSICIAN: Any disease like measles that affects millions of individuals is a significant public health problem. It may not seem like a big deal to people in the United States, where it is a somewhat uncommon childhood disease. Most children who get it develop an itchy red rash and miss a week of school. Then, they are immune. But measles is a major killer in developing countries where there are not enough vaccination programs and there is poor medical care and poor general nutrition. We have an excellent vaccine that could eliminate the virus just as we have eliminated smallpox. We would use the grant money to prepare and distribute measles vaccine globally as part of a coordinated effort to wipe out the measles virus.

Segment 4: Proposal 3

Hospital Administrator's Office

HOSPITAL ADMINISTRATOR: Patients come to our hospital for routine surgery and then, five days later, they have a life-threatening infection of *Staphylococcus aureus*. But that's not new. *Staph* is everywhere, especially in hospitals where infants, surgical patients, and others in poor health provide an environment with plenty of easy prey for the bacteria. What's changed is that the antibiotics that once cured a *Staph* infection are not effective anymore. We're lucky, because we have vancomycin, which kills the most resistant strains of *Staph aureus*. But recently, we've discovered isolated cases of vancomycin-resistant *Staph aureus* (or VRSA). We must work quickly to develop new drug therapies before these resistant strains become widespread. Our proposal is to develop and test drug therapies that can stop *Staph aureus* before we have an epidemic.

Reference Database—AIDS

AIDS—Cause

AIDS is caused by the human immunodeficiency virus (HIV). HIV attacks particular cells of the victim's immune system. As a result, the person's immune defenses are weakened tremendously, and the victim is unable to fight off infections. Even worse, the victim is left vulnerable to many serious diseases, such as tuberculosis, pneumonia, fungal infections, and cancer. Death usually occurs as a result of one of these diseases.

AIDS—Cost

The economic cost of the AIDS epidemic is staggering. First, there is the cost of caring for one patient with AIDS. The most common treatment in the United States is a "cocktail," or mixture, of drugs that can cost up to \$15,000 per patient per year. These drugs slow the progress of the disease, but do not eliminate HIV from the patient's body. Research also shows that these drugs must be taken regularly from the time of diagnosis for the rest of the patient's life: As soon as the drugs are stopped, the virus bounces back, as dangerous and life threatening as ever. A further drawback is that the virus in a patient may become resistant to these drugs.

In the United States alone, the cost of providing these drugs to AIDS patients is in the millions of dollars and is rising each year. Unfortunately, developing nations cannot afford to treat their HIV-infected citizens with these drugs. African nations have an average of \$10 per year per person for medical care, yet Africa is the part of the world that is hardest hit with the disease.

The epidemic has other costs, too. In some countries, such as Uganda, Zambia, and Zimbabwe, three-fourths of the hospital beds are filled with children who are HIV-positive. Millions of adults have died, and many of them have left orphaned children. Many others have left surviving spouses who also are ill, need treatment, and cannot work. Families cannot find money to pay for funerals, and employers must find and train new employees. This problem is eating away at these countries' economies.

As one scholar described the problem, "The epidemic's direct and indirect consequences are wiping out the gains that many of these countries have made in the past 30 years."

AIDS—Death Rate

The total number of worldwide deaths from AIDS in 1998 was estimated to be 2.5 million (2 million adults and 510,000 children under the age of 15).

The total number of worldwide deaths since the beginning of the epidemic is estimated to be 13.9 million (10.7 million adults and 3.2 million children under the age of 15).

AIDS—Definition

AIDS, acquired immune deficiency syndrome, is a disease in which the immune system no longer functions effectively. It is caused by the human immunodeficiency virus (HIV). People with AIDS are vulnerable to a variety of other diseases (opportunistic infections) that only rarely occur in people with healthy immune systems.

AIDS—Diagnosis

If a person is infected with HIV, his or her body will make antibodies, special proteins produced by the immune system that recognize and can attach to HIV. To test for HIV infection, doctors look for these antibodies in the person's blood. If antibodies against HIV are present, they are evidence that the person is infected with HIV. If antibodies against HIV are not present, the person either is not infected, or was infected recently enough that his or her body has not yet made these antibodies in detectable quantities. Only another test at a later date can distinguish between these possibilities.

Infection with HIV is not the same as having AIDS. When a physician suspects that a person may have AIDS, he or she may order another laboratory test of the person's blood. The diagnosis of AIDS is confirmed if the person's CD4 T-cell concentration is lower than 200 cells per cubic millimeter of blood (normal levels are at least 800 cells per cubic millimeter of blood), or if the person develops one or more of the opportunistic infections associated with AIDS.

AIDS—Incidence (Predictions)

Scientists are predicting that in the short term, the international epidemic of AIDS will become worse, especially in the developing countries of Africa and Southeast Asia. The spread of the epidemic means that the already enormous burden of caring for the ill will only increase.

In contrast, scientists are predicting that in the United States and other industrialized countries, the epidemic will slow, at least for some populations. HIV infection, however, likely will continue to rise in certain populations (especially the poor and disadvantaged).

The cost of care also will rise significantly, as more people who today are HIV-positive develop AIDS.

AIDS—Incidence (United States)

In the United States, there are more than 1 million people who are HIV-positive. Each year, approximately 50,000 more people are infected, including about 2,500 infants. AIDS is now the leading cause of death for men between the ages of 25 and 44, and the fourth highest cause of death for women in this age category.

Whereas the death rate from AIDS and the rate of HIV infection are declining overall in the United States and other industrialized countries, it is not declining—and, in some cases, may be increasing—among certain groups of people, including teenagers, women, and people over the age of 50.

AIDS—Incidence (Worldwide)

More than 40 million people worldwide have contracted the human immunodeficiency virus (HIV) since the early 1980s, and nearly 14 million have died of AIDS. About 28 million people currently have AIDS or are infected with HIV, and about 16,000 more people are infected with HIV every day. In 1998 alone, an estimated 2.5 million people died of AIDS, 510,000 of them children.

Worldwide, the highest incidence of HIV infection is in sub-Saharan Africa. Two-thirds of all HIV-positive people and 90 percent of all infected children live in this area. In some African countries, 1 in 4 adults is HIV-positive.

The second highest incidence of HIV infection is in Southeast Asia. Here, the epidemic is worst in India and Thailand.

AIDS—Modes of Infection

You can get HIV (the virus that causes AIDS) from any person who is infected with the virus, even if he or she does not look sick, does not know he or she is sick, and does not yet test positive for the virus (is not yet HIV-positive).

Most people get HIV by

- having unprotected sex with a person who is infected,
- sharing a needle (shooting drugs) with a person who is infected, or
- being born from or drinking the breast milk of a woman who is infected.

There are no known cases of someone getting HIV through contact with an infected person's tears or saliva, but it is possible to catch HIV through oral sex, especially if you have open sores in your mouth or bleeding gums.

In the past, some people were infected with HIV from getting a blood transfusion from an infected person. Today, the blood supply is carefully tested, and the risk of infection from a blood transfusion in the United States is very low.

AIDS—Name

The name "AIDS" means "acquired immune deficiency syndrome."

The word "acquired" means that a person can catch AIDS, that is, that it is an infectious disease.

The words "immune deficiency" mean that the disease causes a weakness in a person's immune system. The immune system is the part of the body that fights disease.

The word "syndrome" is a medical term for a group of health problems that all are associated with a particular disease. People with AIDS display many health problems, such as weight loss, problems with infections, brain tumors, and other health problems.

AIDS—Treatment (General Information)

There is still no cure for AIDS. There are drugs available that can slow down the damage to a person's immune system and slow down the multiplication of the virus. But there are no drugs yet that eliminate HIV completely from a person's body.

Some scientists think that the new, strong, anti-HIV drugs that are currently available might eliminate all the HIV from a person's body if the drugs were taken for several years, but there are no known cases in which this has happened yet.

There are some drugs available that a person can take to prevent some of the opportunistic infections that people with AIDS are susceptible to. There is little that a person can do to prevent some of the other infections.

AIDS—Treatment (Drug Therapies - General Information)

The best and most widely used treatment for AIDS today is designed to slow down a person's progression from being HIV-positive to having AIDS. This treatment involves taking a "cocktail," or mixture, of several drugs that suppress the multiplication of the human immunodeficiency virus (HIV), which slows down the damage to a person's immune system.

The use of these drugs has led to a 44 percent decline in AIDS deaths in the United States, as well as to a significant drop in the number of cases of opportunistic infections among AIDS patients. These drugs do not, however, cure AIDS, because they do not completely eliminate HIV from a person's body.

Following this treatment plan correctly is a challenge for patients. The cost of these drugs is about \$10,000 to \$15,000 per year per patient. Side effects include nausea, diarrhea, rashes, headaches, and elevated triglyceride and cholesterol levels in the blood. Patients must take a minimum of eight pills every day, some of which must be taken on an empty stomach, some with food, and some with or without other pills. If patients miss doses, they risk not completely suppressing the multiplication of the virus and also risk the appearance of strains of HIV that are resistant to the drugs.

AIDS—Treatment (Drug Therapies - Viral Resistance)

When drugs against HIV do not work, it is often because the virus has become resistant to one of the drugs being used. This resistance is the result of mutations that occur in the viral genes.

Unfortunately, use of anti-HIV drugs can actually promote the reproduction of resistant virus particles. Untreated, HIV makes approximately 10 billion new virus particles every day in an infected person. But HIV does not copy its genetic material very accurately. Because of its sloppy replication, each one of these new virus particles may be different from the parent virus in one or more genes. And because so many virus particles are produced each day, it is very likely that at least one virus is produced each day that is resistant or partially resistant to one of the antiviral drugs the person is taking. This virus particle now has an advantage over other virus particles that are not resistant to the drug, and may reproduce faster than nonresistant strains. Thus, taking anti-HIV drugs can actually promote the reproduction and accumulation of viruses that are not inhibited by the drugs the patient is taking.

Because resistance can occur so easily and because no single drug on the market can inhibit HIV reproduction completely on its own, physicians now treat patients with mixtures (cocktails) of drugs. Physicians also must stay on the lookout for signs of viral resistance emerging in a patient, and if resistance appears to be emerging, must consider new combinations of drugs that will be effective for that patient.

HIV—Course of Infection

Many people do not know when they are first infected by HIV because they have no symptoms. Other people don't know because although they get a fever, a headache, and sore muscles and joints for one or two weeks, they think that it is just the flu.

The virus multiplies inside the victim's body for a few weeks (or even a few months) before his or her immune system responds. During this period of time, the person is infected with HIV and can infect others, but he or she won't test positive for HIV.

When a person's immune system begins to respond to the virus by making antibodies, the person will test positive for HIV.

Some people with HIV stay healthy for many years after infection. During this time, however, the virus is damaging the person's immune system. Health care professionals can measure this damage by counting the number of CD4 T-cells a person has. These cells, also called T-helper cells, are part of a person's immune system. Healthy people have between 500 and 1,500 CD4 T-cells in each cubic millimeter of blood, but people with HIV disease have many fewer. As a person's CD4 T cell count goes down, he or she may start having signs of HIV disease (for example, fevers, night sweats, diarrhea, weight loss, or swollen lymph nodes).

HIV disease is diagnosed as AIDS when the person's CD4 T-cell count drops below 200 CD4 T-cells per cubic millimeter of blood or when the person gets one of the opportunistic infections identified by the Centers for Disease Control and Prevention as characteristic of AIDS.

AIDS progresses at different rates in different people. Some people die within five years of being infected with HIV, whereas other people live for many years, even after they develop AIDS. With treatment, the average time to death after being diagnosed is ten years in the United States; without treatment the average time to death is two years.

HIV—Definition

HIV stands for "human immunodeficiency virus." HIV is the virus that causes AIDS.

HIV—Definition of HIV-Positive (or HIV Disease)

When a person is infected with HIV, his or her body responds by making antibodies against the virus. (Antibodies are special proteins that fight disease.) Blood tests for AIDS look for antibodies in the blood against HIV. People who have antibodies against HIV in their blood are said to be "HIV-positive." They also might be said to have "HIV disease."

Being HIV-positive (or having HIV disease) is not the same as having AIDS. Many people are HIV-positive, meaning that they have been infected with HIV, but they are not yet sick. As HIV remains in the body, it slowly wears down the immune system.

HIV—Rate of Mutational Change

Untreated, HIV reproduces very rapidly inside a person's body, making approximately 10 billion new virus particles every day. But HIV does not copy its genetic material very accurately. In fact, because of its sloppy replication, each one of these new virus particles may be different from the parent virus in one or more genes. Thus, HIV shows a very rapid rate of mutational change.

The result of this high rate of mutational change is that there exist many different HIV strains, not only in the world, but even within one person's body. This presents a problem for developers of new drugs to combat HIV (some of these different strains may be resistant to the drug) and for developers of vaccines against HIV (the vaccine may be effective against one strain of HIV but not against another).

Reference Database—Measles

Measles—Definition

Measles (also called rubeola) is a severe and highly contagious viral infection of the respiratory tract, although its most prominent symptom is a skin rash.

The measles virus spreads by direct contact with an infected person. Usually, the virus spreads via droplets of fluid from the person's respiratory tract. These droplets contain millions of virus particles that can infect another person, entering through the respiratory tract. Here, the virus incubates for one to two weeks before symptoms appear: fever, discomfort, sore throat, coughing, and finally a painful and itchy rash. After a few more weeks, the infection usually subsides. In a few cases, infection leads to pneumonia, brain damage, ear and sinus infections, convulsions, and sometimes death.

In developed countries, measles usually is not a fatal disease. In many developing countries, however, measles has a much higher mortality rate, accounting for 10 percent of all deaths in children under age 5.

Measles—Diagnosis

People who have measles show a variety of symptoms, ranging from mild fever to severe skin rashes, to life-threatening seizures and infections. Doctors diagnose measles by the presence of Koplik's spots—tiny, white specks, surrounded by a red halo, that appear on the inside of the cheek, near the molars. Doctors also can use blood tests to check for antibodies against the measles virus.

Measles—Epidemics

Measles epidemics occur when the measles virus spreads rapidly through a susceptible population. Epidemics pose the greatest threat to unvaccinated people or people who have had only one dose of the vaccine and failed to develop antibodies against the virus.

Populations with high vaccination rates are less susceptible to epidemics. However, such populations can experience measles outbreaks in which three or more linked cases of the disease occur. Outbreaks are shorter in duration and more limited in transmission than epidemics.

The higher the percentage of unvaccinated people, the more susceptible a population is to an epidemic. The "epidemic threshold" is the point at which the percentage of unvaccinated people is high enough to risk an epidemic.

Measles—Immunity

There are three kinds of immunity to measles: passive immunity, natural immunity, and immunity derived from vaccination. Infants born to mothers who have either had measles or been vaccinated are protected by maternal antibodies; that is, they have passive immunity. This protection lasts six months on average, and then the child becomes susceptible to measles. A person is naturally immune if he or she has had contact with the measles virus and has developed antibodies against it. People born before 1957 are considered naturally immune because of the high probability that they were exposed to the virus during childhood. People born after 1957 are considered immune if they have been fully vaccinated, have had a confirmed case of measles, or have had blood tests that confirm previous exposure to the virus. Full vaccination

requires two doses of vaccine: one between the ages of 12 to 18 months, and the other between the ages of 4 to 6 years or 11 to 12 years. (The second dose helps catch the small number of people who do not become immunized by the first dose.)

Measles—Incidence (Historic)

During this century, there has been a dramatic decrease in measles epidemics. Prior to the development of the measles vaccine, 5.7 million people died each year from measles. (Some historians have suggested that measles might have contributed to the decline of the Roman Empire.)

In 1920, the United States had 469,924 measles cases and 7,575 deaths due to measles. From 1958 to 1962, the United States had an average of 503,282 cases and 432 deaths each year. (Measles reporting began in 1912; prior to this time, no statistics are available.) In large cities, epidemics often occurred every two to five years.

When the measles vaccine came on the market in 1963, measles began a steady decline worldwide. By 1995, measles deaths had fallen 95 percent worldwide and 99 percent in Latin America. In the United States, the incidence of measles hit an all time low in 1998, with 89 cases and no deaths reported.

There have been several epidemics in the United States since 1963: from 1970 to 1972, 1976 to 1978, and 1989 to 1991. The epidemic of 1989–1991 claimed 120 deaths out of a total of 55,000 cases reported. Over half of the deaths occurred in young children.

Measles—Incidence (United States)

In 1997, the Centers for Disease Control and Prevention (CDC) reported a total of 138 cases of measles in the United States. Most of these outbreaks probably began when an infected person from another country (specifically Germany, Italy, Switzerland, Brazil, and Japan) entered the United States. The virus subsequently spread through the population, with the longest chain of transmission lasting five weeks. Children were most affected by these outbreaks: 29 percent of cases were children 1–4 years; 28 percent were children 5–19; 26 percent were adults 20–39. In addition, unvaccinated people accounted for 77 percent of cases; people who received only one dose of vaccine accounted for 18 percent of cases; and people who received the full two doses of vaccine accounted for 5 percent of cases. (These statistics demonstrate that a small percentage of people fail to develop immunity after one or even two doses of vaccine.)

In 1998, the United States had only 89 cases and no deaths due to measles. Measles cases clustered in a few states. Arizona, California, Florida, Massachusetts, Minnesota, New York, Pennsylvania, South Dakota, and Texas reported 64 percent of measles cases in 1997. Most of these cases were from foreign visitors who brought the virus with them or from U.S. citizens who contracted the virus while traveling abroad. These patterns suggest that there is no established measles virus circulating in the United States.

Measles—Incidence (Western Hemisphere)

The Western Hemisphere (countries in the Americas and the Caribbean) have the lowest incidence of measles worldwide, with only 2,109 cases reported in 1996. However, low rates of vaccination among some populations resulted in several outbreaks: in 1997 in Brazil (51,000 cases); in 1998 in Argentina (3,000 cases and 11 deaths); and in 1998 in Bolivia (111 cases). Children under 4 were most commonly affected by these

outbreaks. An outbreak at a Canadian university also suggested that low immunization rates among students had left an opening for the measles virus. In all cases, gene sequencing indicated that the virus had come from a foreign source.

Measles—Incidence (Worldwide)

According to the World Health Organization (WHO), there were 31 million cases of measles in 1997, resulting in almost 1 million deaths. (These figures are estimates because only a fraction of measles cases worldwide are actually reported.) The majority of these cases occurred in Africa, followed by Asia, India, and the Middle East. In fact, in 1997 roughly 99 percent of all measles deaths occurred in developing countries.

In 1990, measles was the eighth leading cause of death. In 1997, it was the sixth leading cause. According to some analyses, this represents a greater loss of life than that caused by AIDS and almost as great a loss as that caused by malaria. The majority of deaths occur among young children. In developing countries, measles accounts for 10 percent of all deaths in children under age 5.

Measles—Transmission (General)

Some reports claim measles is the most contagious of all infectious diseases. The measles virus spreads easily by direct contact. Usually, this happens when infected people exhale minute droplets containing the virus particles; these droplets come in contact with other people and cause infection. In addition, people who have had the disease sometimes have low levels of virus for many decades following. These viruses also can infect other people.

Scientists use gene sequence data to determine origin and transmission patterns of the measles virus. If the virus is established and circulating among members of a population, it is said to be endemic or indigenous. Currently, the virus is endemic in many African, Asian, and European countries. The Western Hemisphere has no endemic measles virus, and the only outbreaks occur when visitors and foreign travelers carry the virus from other countries.

Measles—Transmission (Reservoirs of Infection)

Although the measles virus has been eliminated from the Western Hemisphere, there are reservoirs of the measles virus in many countries around the world (for example, in Africa, Asia, and Europe). Because of widespread travel, it is impossible to isolate measles by country or hemisphere. As recent cases in the Western Hemisphere show, outbreaks can still occur despite the absence of any established virus in a population. (High levels of immunization prevented the virus from becoming re-established through an epidemic.) Until eradication efforts succeed globally, countries must maintain high rates of vaccination in order to protect their populations.

Fortunately, there is no reservoir of the measles virus in animals. Unlike some viruses, the measles virus is specific to humans and cannot survive or replicate in any other animal species. If the virus is eradicated in the human population, there are no animal reservoirs that could reintroduce the virus.

Measles—Treatment

Measles has a severe effect on the nutritional status of a child: well-nourished children who are otherwise healthy lose weight when they have the measles, while malnourished children become seriously ill. Treatment for measles consists of bed rest, medicines to control fever, and calamine lotion or other salves to relieve itching. Mortality rates are low in most developed countries where children have relatively good nutrition; however, complications occur rarely that require hospitalization: pneumonia, appendicitis, and severe infections of the brain or respiratory systems. In many developing countries where conditions of poor nutrition, poor sanitation, and lack of adequate health care are common, measles mortality rates are considerably higher, especially among children.

Measles—Vaccine (Definition)

Measles vaccine (also called the Measles Virus Vaccine Live) is an inactivated form of the measles virus. The measles vaccine came on the market in the United States in 1963. In the United States, children usually receive a combined measles, mumps and rubella vaccine (MMR).

The measles vaccine causes the body to produce antibodies against the virus, providing lifelong protection from the active virus. To ensure immunization, a person usually receives two doses of the vaccine: One dose at roughly 1 year of age and a second dose between 4 and 6 years of age or between 11 and 12 years of age. One dose of vaccine is only 95 percent effective (95 percent of people develop antibodies and become immune, whereas 5 percent fail to develop antibodies). The second dose helps catch the small number of people who do not develop antibodies after the first dose.

Measles—Vaccine (Risks)

More than a decade of studies have shown little or no serious side effects associated with the measles vaccine. Those with a presumed higher risk of side effects include: people with a history of allergic reactions to previous measles vaccine, the antibiotic neomycin, or other substances such as gelatin; pregnant women; infants younger than 6–12 months; people taking certain medications or receiving X-rays or cancer therapies; and people with immune deficiencies or severe illness with fever.

One 1998 study suggested a link between the measles vaccine and chronic bowel disease and autism, a developmental disorder. Reviews of this study, however, failed to confirm a cause-effect relationship. Additional studies of 3 million vaccinated children also showed no increased risk between the measles vaccine and severe adverse effects. Several independent groups, including the World Health Organization (WHO), found no severe effects associated with the vaccine despite more than 10 years of research.

Measles—Vaccine (Side Effects)

The measles vaccine sometimes causes a range of mild side effects including low-grade fever, skin rash, itching, hives, swelling, reddening of skin, and weakness. Rarely, the vaccine causes seizures, double vision, headaches, vomiting, joint pain, or pain in the digestive system.

Eradication—Benefits

The ultimate benefit of eradication is the prevention of an estimated 1 million deaths in children each year. Eradication also saves money in the long run, as the case of smallpox demonstrates. When smallpox was eradicated in 1977, countries discontinued vaccination and prevention efforts. This meant an enormous savings in medical costs: By 1985, the United States was recovering the money it had invested in global eradication every 26 days. As with smallpox, money spent on measles eradication would eventually be recouped from savings in vaccination programs and medical treatment for measles patients.

Eradication—Challenges

Despite recent successes, several challenges remain in the fight for global eradication of measles. The magnitude of vaccination programs is staggering: Every day in the United States 11,000 children are born, each requiring 15–19 doses of different vaccines by the time they are 1½ years old. It is logistically impossible to ensure that 100 percent of these children are vaccinated. Instead, vaccination programs can only aim to eliminate the risk of a major epidemic; this goal can be achieved for measles with a 90 to 95 percent vaccination rate.

In developing countries, the eradication challenge is even greater because lack of funds results in minimal health care programs and inadequate surveillance. Because cost effectiveness is critical in these countries, vaccination programs must target the most needy populations. For example, in countries with a high incidence of measles and a low vaccination rate, school-age children are likely to have developed a natural immunity to the virus (due to previous contact with the virus). These countries should target vaccination programs at a narrow age range, focusing on young children (who are less likely to have had previous contact with the virus). In contrast, countries like the sparsely populated Sahel of West Africa have a lower incidence of measles, and therefore many potentially susceptible adults. In this case, vaccination programs should best target a wider age range.

As campaigns succeed in eliminating measles from one country after another, experts predict that patterns of outbreaks and risks will shift. For example, older children and adults will be more likely to be susceptible; infants born to vaccinated mothers will be protected by maternal antibodies for a shorter period of time; people might become complacent about having their children vaccinated; and the number of susceptible people might increase, approaching the threshold level for epidemics. These changing patterns might require changes in vaccination strategies.

Eradication—Costs

Estimates of the cost of global measles eradication run as high as \$4.5 billion by the year 2010, an amount that includes \$1.7 billion for vaccines in developing countries. In 1998 alone, the Centers for Disease Control and Prevention (CDC) budgeted \$8 million for international programs to eliminate measles.

The measles vaccine itself is relatively inexpensive. (For countries in the Pan American Health Organization, each dose costs just 10 cents.) Eradication, however, requires additional expense and effort. These include extensive surveillance systems, education and health campaigns, and systems to ensure quick response to contain outbreaks. These expenses weigh heavily on some developing countries, whose health care systems are already stretched to their limits.

Eradication—Definition

The goal of eradication efforts is to stop the global spread of the measles virus and thereby end the need for vaccination. Eradication is possible because there is a highly effective vaccine and the measles virus survives or replicates only in humans. This means that there is no hidden reservoir of the virus in animals that could lead to outbreaks in humans in the future.

To achieve global eradication, all countries must first eliminate any measles viruses that are established or circulating within the population. These elimination campaigns require ongoing surveillance and vaccination to prevent outbreaks from measles viruses imported from other countries.

Eradication—Feasibility

In 1996, the World Health Organization (WHO) confirmed that global eradication of measles is feasible between 2005 and 2010 using current vaccines. To do so, they urge that all countries: (1) use a two-dose strategy for immunization; (2) include rigorous diagnosis and surveillance; (3) view measles outbreaks as an opportunity to raise awareness and political support for eradication; and (4) work closely with other countries. Moreover, the WHO urges developing countries to link their measles and polio vaccination efforts to prevent conflicts over limited resources.

Eradication—Problems

Because of limited resources and logistical problems delivering the vaccine, measles remains a serious problem in some developing countries. Experts warn that vaccine shortages may prevent these countries from effectively controlling outbreaks. They also warn that measles vaccination programs compete with polio eradication efforts in some countries, making it difficult to make progress against either disease.

Some experts believe that the United States has become complacent in its attitude toward measles. They say that the United States views measles as a mild disease and focuses on the safety and effectiveness of vaccinations rather than on maintaining vaccination coverage so that global eradication can be achieved. These experts believe that by delaying eradication efforts, many of the hard won gains of the past decade will be wiped out.

Eradication—Campaigns (Western Hemisphere)

In 1994, countries in the Western Hemisphere set a goal of eliminating measles by the year 2000. From 1987 to 1994, numerous countries supplemented their routine vaccination programs with catch-up campaigns. All these countries now have laboratories that can report data to a regional surveillance network. As a result, in 1996 over half of the countries exceeded 90 percent vaccination coverage. That year saw a total of 2,109 cases of measles, a record low. This represents only 0.3 percent of the global total of measles cases. In addition, more than 60 percent of the countries in the Western Hemisphere reported no cases of measles.

Eradication—Campaigns (Worldwide)

Support for global measles eradication began to form in 1989, when the World Health Assembly set a goal for 1995 of decreasing measles deaths by 95 percent compared with measles deaths during the prevaccination period. In 1990, the World Summit for Children resolved to vaccinate 90 percent of children by the year 2000. Countries in the Western Hemisphere, Europe, and the Eastern Mediterranean formed organizations to pursue regional goals.

Current data suggest that vaccination programs have eliminated the measles virus from much of the Western Hemisphere, the United Kingdom, and the West Bank and Gaza. Countries in Europe, the South Pacific, the Middle East, and Southeast Asia have increasingly used catch-up vaccination programs to supplement their routine vaccinations. These campaigns reached an additional 32.8 million children. As of 1998, catch-up programs are continuing in Australia, the Philippines, Romania, and Tunisia.

Eradication—Surveillance

Surveillance is a critical component of measles eradication. Measles surveillance requires local, regional, and national efforts. Locally, doctors must work with microbiology labs to diagnose measles cases correctly. Regional and national laboratories then gather and analyze this data to determine the original source of the virus, how many other people might have come in contact with it, and how it might best be contained. Surveillance networks also monitor vaccination rates to determine the locations of populations especially at risk for measles epidemics. Without this data, measles elimination would not be possible, as countries could not see how best to use scarce resources of money and technology. Although most developed nations have adequate surveillance networks, many developing countries have only one national laboratory dedicated to the problem of measles elimination.

Vaccination—Programs (At-Risk Populations)

In the United States, populations at risk for reduced levels of vaccination include people of low income, minority groups, large families, and young mothers. People at risk for contracting measles include those living in the inner city or an area of a previous measles outbreak, women of childbearing age, college students, foreign travelers, and health care workers.

People who receive only one dose of vaccine are also at higher risk for contracting measles. In 1999, an outbreak in Anchorage, Alaska, started when a 4-year-old child, visiting from Japan, developed a measles rash. A month later, students at a local high school started coming down with the disease. A total of 33 cases were reported, with no deaths. Despite a high immunization rate at the school, the outbreak occurred because half of the students had only had one dose of the vaccine. One dose is only 95 percent effective. This left a window of opportunity for the virus. Of the 33 cases, 29 were students who received at least one dose of vaccine. Afterward, school and health officials accelerated second-dose vaccinations in order to prevent future outbreaks.

Vaccination—Programs (Costs)

Costs of measles vaccination programs vary depending on the strategy and goals of the program. In 1998, the Australian government budgeted \$30 million for a vaccination program to immunize 95 percent of its children. The actual price for the measles vaccine varies. In the Americas, the vaccine is available at a cost of 10 cents per dose or 49 cents per dose if combined with the vaccines for mumps and rubella (German measles)—the MMR vaccine.

Cost estimates also must acknowledge that vaccination programs can lead to a decrease in medical costs for treating measles patients. According to one estimate, every \$1 spent on measles vaccine saves \$10.30 in medical costs and \$3.20 in indirect or social costs.

Vaccination—Programs (Definitions)

In addition to routine vaccinations, there are three different types of vaccination programs, each with a different strategy and goal. Catch-up programs are one-time campaigns that aim to vaccinate all children 9 months to 14 years, whether or not they have had measles or previous vaccinations. Keep-up programs are routine services that focus on vaccinating at least 90 percent of children at age 12 months in the years following the catch-up program. Follow-up programs take place at least once every four years and aim to vaccinate all children ages 1–4.

Vaccination—Programs (Challenges)

Public fears about possible adverse effects of the measles vaccine decrease vaccination rates. A study showed that in Wales, United Kingdom, vaccination rates fell roughly 14 percent (from 83 percent to 69 percent) after adverse publicity about the measles vaccine raised concern that the vaccine might cause chronic bowel disease or autism. However, intense scientific scrutiny has not confirmed any link. Experts warn that if such a decline in vaccination rates continues, it could undo recent progress that has almost eliminated measles in the United Kingdom.

Some researchers note that as the threat of measles declines, parents' concerns over safety take on greater importance. In Australia, of 1.1 million students offered immunization, only 86 percent received parental consent. In Chicago, the same populations that had suffered the highest incidence in a previous measles epidemic remained undervaccinated five years later. Even a free, mobile vaccination program had not increased vaccination rates to acceptable levels: More than 45,000 children in Chicago were still vulnerable to measles. Community outreach and education programs might improve this situation.

Vaccination—Rates (United States)

To prevent measles outbreaks, scientists estimate that 95 percent of the population must be immune. In the United States, vaccination rates are at record levels: Coverage exceeded 90 percent for children roughly 1½–3 years old and 95 percent for children ages 5–6 years. However, pockets of low immunization persist. In Chicago in 1994, coverage for children was 47 percent overall but only 29 percent for inner city, African-American children. This occurred despite access to free vaccines and a measles outbreak in Chicago in 1989 that heightened awareness. Another study of young children in rural New York found that only 85 percent

were vaccinated. And, according to the Centers for Disease Control and Prevention (CDC), just over one-half of all schoolchildren in the United States have had both doses of the vaccine. Note that one dose is only 95 percent effective. (Ninety-five percent of people with one dose will gain immunity; the other 5 percent will fail to develop antibodies and will be unprotected.) Even when both doses are given, some people fail to form antibodies, although the probability of this happening is extremely low.

Vaccination—Rates (Western Hemisphere)

In 1997, there was a resurgence of measles epidemics across the Americas, mainly in Brazil and Canada. In these countries, vaccination rates had fallen among some populations, making them more susceptible to epidemics. Gene sequence data indicate that most of these outbreaks resulted from strains of measles virus imported from Europe and Asia that subsequently spread among unvaccinated or undervaccinated populations. This suggests that, despite the absence of established measles virus, populations can still be at risk for epidemics.

Vaccination—Rates (Worldwide)

Eradication is only feasible if all countries eliminate all of the measles virus. Elimination requires that at least 90 percent and possibly as much as 95 percent of a population have immunity. At this time, all countries in the Western Hemisphere have achieved this goal, with vaccination rates over 90 percent.

Worldwide, however, vaccination rates are only 82 percent. Rates are highest (93 percent) in the Americas and the Western Pacific. Rates are lowest (57 percent) in Africa; 10 African countries have rates of less than 50 percent. Moreover, 57 percent of the world's children live in areas with vaccination rates below 50 percent. More than two-thirds live in Africa or Southeast Asia.

In 1997, several vaccination campaigns targeted at-risk populations in an attempt to raise overall vaccination rates. These campaigns included five countries in Africa, four in Southeast Asia, and one in the South Pacific region. As a result, more than 5.8 million children were vaccinated.

Reference Database—VRSA

***Staphylococcus aureus* (SA)—Antibiotic Resistance (General)**

Throughout history, *Staphylococcus aureus* (SA) has been a dangerous pathogen once it has successfully breached the normal defense system. The first effective antibiotic against SA, penicillin, came available in the 1940s. Soon after, SA evolved resistance to penicillin, and by the late 1950s, 50 percent of all SA were resistant. Today, fewer than 10 percent of SA infections can be cured with penicillin.

The next weapons against SA, methicillin and cephalosporins, came available in the 1960s and 1970s. By the late 1970s, some strains of SA had evolved resistance to these drugs. Today, as many as 50 percent of SA isolated from U.S. hospitals are resistant to methicillin.

The last effective defense against methicillin-resistant SA (called MRSA) is vancomycin. However, the increasing use of vancomycin has set the stage for the evolution of vancomycin-resistant SA (called VRSA). Antibiotic use and resistance represent a vicious cycle: The more doctors use vancomycin, the more they create an environment that encourages the evolution of VRSA.

***Staphylococcus aureus* (SA)—Antibiotic Resistance (MRSA)**

MRSA, or methicillin-resistant *Staphylococcus aureus*, are strains of the bacterial pathogen *Staphylococcus aureus* (SA) that have evolved resistance to the antibiotic methicillin. These strains are also likely to be resistant to other antibiotics used to treat SA infections. MRSA strains first appeared in the late 1970s and currently 40-50 percent of SA isolated from U.S. hospitals are resistant to methicillin. These infections are treated with the powerful antibiotic vancomycin. Scientists hypothesize that the strains of SA most likely to evolve resistance to vancomycin are the MRSA.

***Staphylococcus aureus* (SA)—Antibiotic Resistance (VRSA)**

Scientists expect strains of the bacteria *Staphylococcus aureus* (SA) that are fully resistant to the antibiotic vancomycin to evolve soon. Vancomycin-resistant *Staphylococcus aureus* (VRSA) is the term used to describe these strains. The expected emergence of VRSA is alarming because vancomycin is the only antibiotic that is effective against MRSA, strains of SA that are resistant to the antibiotic methicillin (MRSA).

Although VRSA—strains of SA that are fully resistant to vancomycin—do not currently exist, medical workers have recently isolated strains of SA that are four times more resistant to vancomycin than SA strains found previously. Because infections due to these strains do not respond to the usual doses of vancomycin, many physicians and other experts incorrectly refer to them as VRSA. They should be described as SA strains with intermediate resistance to vancomycin. Infections due to these strains can be cured using higher doses of vancomycin.

***Staphylococcus aureus* (SA)—Definition**

Staphylococcus aureus (SA) is a bacterium that is commonly found on the skin and in the eyes, nose, and throat of animals and humans. SA is one of the most common causes of infections worldwide. Though not a problem for healthy adults, SA is potentially virulent and can cause serious infections of the skin,

eyes, brain, blood, and respiratory and digestive tracts, as well as bone and connective tissue. Some SA infections, such as bacteremia, have death rates of 40 percent.

***Staphylococcus aureus* (SA)—Risk Factors**

Although the body's defenses must be weakened or breached before *Staphylococcus aureus* (SA) bacteria cause disease, many people are potential victims of SA infections. SA enters the body through wounds such as burns, deep cuts, or surgical incisions. People whose immune systems are weakened from bouts with other diseases—hospital patients with influenza, leukemia, skin disorders, or diabetes, or patients recovering from kidney transplants—are vulnerable. Patients receiving radiation or chemotherapy also are more susceptible to SA infection. In 1992, nearly 1 million of the 23 million U.S. citizens who had surgery developed infections, most of them due to SA. Likewise, SA poses a threat to newborns, whose immune systems are not yet fully functioning.

***Staphylococcus aureus* (SA)—Transmission**

Because *Staphylococcus aureus* (SA) bacteria can survive dry conditions, they remain alive for long periods of time on dust particles, clothing, furniture, or hospital equipment. SA is able to grow with or without oxygen. This allows the bacteria to survive the aerobic conditions of the skin or nasal passages, waiting for an opportunity to invade deeper tissues. Once inside, SA can produce powerful toxins that further destroy and disrupt the body's tissues. SA also can resist immune system cells that engulf and destroy invading bacteria, making it a formidable adversary for the immune system.

A high percentage of hospital workers are passive carriers for SA, harboring the bacteria on their skin and in their upper respiratory tracts without showing any symptoms. For this reason, SA often spreads from patient to patient via the hands of hospital workers. SA also spreads via dust, clothing, furniture, or medical equipment that has been in contact with infected patients.

Antibiotic Resistance—Cost

As more and more strains of disease-causing bacteria become resistant to commonly used antibiotics, physicians must switch to other, often more expensive drugs. For example, switching from the penicillins to methicillin in the treatment of *Staphylococcus aureus* (SA) infections increased treatment costs about 10-fold.

It is difficult to assess the overall cost of antibiotic resistance. A report from the Government Accounting Office indicates that no federal agency adequately monitors antibiotic resistance or evaluates its social and financial costs. One estimate, however, places the annual cost of antibiotic resistance as high as \$5 billion per year.

Antibiotic Resistance—Definition

Antibiotic resistance describes the condition of bacteria whose growth and reproduction is unaffected by particular antibiotics. Bacteria have a variety of mechanisms for evading the toxic effects of antibiotics. In some cases, the bacterial cell membranes are altered so that an antibiotic cannot enter the cell. In other

cases, resistant bacteria actively pump the antibiotic out of the cell as soon as it enters. Still other resistant bacteria make an enzyme that degrades an antibiotic as soon as it enters the cell. There are also other mechanisms for antibiotic resistance.

Mutations in genes that code for particular proteins may result in antibiotic resistance. For example, if an antibiotic uses a particular protein in the cell membrane to enter the cell, a change in that protein (due to a mutation in the gene that codes for it) may prevent the antibiotic from entering the cell. Many genes that result in antibiotic resistance are found on DNA molecules that are easily transferred from one bacterium to another.

Antibiotic Resistance—Evolution

Antibiotic resistance in bacteria evolves by mutations in the bacterium's genes, by rearrangement of the bacterium's genes, or by acquisition of genes that result in antibiotic resistance from other bacteria. Regardless of the way a bacterium becomes resistant to a particular antibiotic, once this has happened, a vicious cycle begins. The resistant bacterium will survive treatment while most of the susceptible bacteria in the population die. After antibiotic treatment is completed, the few surviving susceptible bacteria and the resistant bacterium will reproduce, and the resistant bacterium will pass the gene that provides antibiotic resistance on to its progeny. If the infection recurs, there will now be a larger number of antibiotic-resistant bacteria in the population. Antibiotic treatment will be less successful or may fail completely. Across time, almost all of the bacteria of that type that people encounter will be resistant to the particular antibiotic, and new (and, in many cases, more expensive) antibiotics must be used to treat infections caused by that kind of bacteria.

Antibiotic Resistance—Prevention (Challenges)

Overuse of antibiotics has increased the numbers of antibiotic-resistant bacteria. The Centers for Disease Control and Prevention (CDC) estimates that half of the 100 million courses of antibiotics prescribed annually are unnecessary. This misuse means that bacteria will evolve resistance to common antibiotics sooner, and that doctors will have to use last-resort antibiotics such as vancomycin more and more. Therefore, to delay the development of antibiotic-resistant organisms, the CDC has developed a set of recommendations for appropriate use of antibiotics.

Nevertheless, following the CDC recommendations is challenging. One survey of pediatricians revealed that, during a one-month period, 96 percent of pediatricians polled had been pressured by patients to prescribe antibiotics, even when they were not needed. Another study found that, despite education about appropriate uses of the antibiotic vancomycin, 40-60 percent of vancomycin treatments did not follow the CDC recommendations.

Another challenge for preventing antibiotic resistance is that restrictions on the use of one antibiotic often lead to increases in the use of others. In one hospital, restrictions on the use of the antibiotic cephalosporin not only decreased the incidence of cephalosporin-resistant bacteria but also increased the use of another antibiotic (imipenem). Thus, the number of bacteria resistant to that antibiotic increased.

Antibiotic Resistance—Prevention (Successful Programs)

Several initiatives are underway to promote more careful uses of antibiotics. One hospital in Arkansas created a program to wipe out enterococcal bacteria that are resistant to vancomycin (called vancomycin-resistant enterococci, or VRE) by using strict containment protocols as well as extensive education of staff. For example, some effective precautions can be as simple as handwashing. Though some staff complained that the program was overly complicated and labor intensive, rates of VRE infection declined and the last case of VRE at that hospital was reported in May 1998.

Antibiotic Resistance—Research (Development Costs)

Pharmaceutical companies spend an average \$500 million and 12-15 years doing initial research to design a drug, developing large-scale production of it, conducting clinical trials of the drug's safety and effectiveness, and bringing the drug to market.

Vancomycin-Resistant SA (VRSA)—Definition

The term vancomycin-resistant *Staphylococcus aureus*, or VRSA, describes strains of *Staphylococcus aureus* (SA) bacteria that are resistant to doses of the antibiotic vancomycin at or above 32 micrograms per milliliter. Strains of SA that are killed by doses of vancomycin less than or equal to 4 micrograms per milliliter are considered susceptible to the antibiotic, whereas strains that require vancomycin doses of 8 to 16 micrograms per milliliter for killing are considered to have intermediate levels of resistance.

No strains of VRSA have yet appeared; however, since mid-1996, physicians in Japan, the United States, and Europe have described several cases of SA infections that required vancomycin doses of at least 8 micrograms per milliliter to cure the infection. Some medical workers have inaccurately called these strains of bacteria VRSA; however, they are actually SA with intermediate levels of vancomycin resistance.

Vancomycin-Resistant SA (VRSA)—Diagnosis

Emerging vancomycin-resistant *Staphylococcus aureus* (VRSA) bacterial infections would likely have similar symptoms to *Staphylococcus aureus* (SA) infections, except that the infection would persist after vancomycin drug therapy. Doctors test for vancomycin resistance by taking samples of bacteria from an SA infection, culturing or growing them, and measuring their growth in media containing various levels of vancomycin. SA that are killed by vancomycin at a concentration of 4 micrograms per milliliter are considered susceptible, those that require 8 to 16 micrograms per milliliter for killing are considered to have intermediate resistance, and those that are resistant to vancomycin concentrations at or above 32 micrograms per milliliter are considered fully resistant to the drug. To date, the most resistant SA strains show intermediate rather than full resistance to vancomycin.

Vancomycin-Resistant SA (VRSA)—Evolution

In bacteria, antibiotic resistance evolves by mutations in their genes, by rearrangement of their genes, or by acquiring genes that provide antibiotic resistance from other bacteria. The strains of *Staphylococcus*

aureus (SA) bacteria that have intermediate resistance to vancomycin appear to be the result of mutations in their genes. However, scientists are concerned that SA also might acquire genes for full vancomycin resistance from other bacteria, specifically, vancomycin-resistant enterococci (VRE).

Enterococci are a group of bacteria closely related to *Staphylococcus* species, but they are less virulent than SA. When the first VRE strains appeared in 1986, they spread rapidly through hospitals. Currently about 25 percent of enterococci isolated in U.S. hospitals are VRE. Scientists are especially concerned about VRE because these bacteria could potentially transfer the genes that make them resistant to vancomycin to other species of bacteria. Because of their close relationship, it is highly likely that vancomycin-resistance genes will spread from VRE to SA. Laboratory experiments have already confirmed this possibility.

Vancomycin-Resistant SA (VRSA)—Incidence (Intermediate Resistance)

As of 1999, there have been several cases of *Staphylococcus aureus* (SA) bacterial infections with intermediate resistance to the antibiotic vancomycin reported. The first case was reported in 1996 in Japan, when vancomycin failed to cure a 4-month-old boy who became infected with SA after heart surgery. Despite 29 days of vancomycin therapy, the infection persisted. Although doctors finally stopped the infection using a combination of different antibiotics, they understood that a barrier had been crossed. One researcher underscored the urgency of the situation: “*S. aureus*, a major cause of hospital-acquired infections, has thus moved one step closer to becoming an unstoppable killer.”

Since that time, three independent cases of SA with intermediate resistance to vancomycin have occurred in the United States: in Michigan, New York, and New Jersey. In these patients, doctors resorted to alternative antibiotics. Although they eliminated the infection in two of the patients, all the patients eventually died. (All of these patients were quite ill, so the infection might not have been the critical factor in their deaths.) Individual cases of SA with intermediate resistance also have cropped up in France and Hong Kong.

Vancomycin-Resistant SA (VRSA)—Incidence (Predictions)

There have been only a handful of confirmed cases of *Staphylococcus aureus* (SA) with intermediate resistance to the antibiotic vancomycin. But researchers fear it is only a matter of time until strains of SA that are fully resistant to vancomycin (vancomycin-resistant SA, or VRSA) appear. VRSA will probably appear first in developed countries with the highest rates of vancomycin use, such as the United States.

Although there is no way to predict exactly when VRSA will appear or how rapidly it will spread, researchers can make reasonable estimates using a parallel case: the evolution of vancomycin-resistant enterococci (VRE). Enterococci are harmful bacteria closely related to staphylococci. Until the late 1980s, most enterococci were susceptible to vancomycin. The first case of VRE was reported in 1986 in Europe and then another in 1988 in the United States. Then, between 1989 and 1993, the number of VRE cases in hospital patients increased 20-fold. In New York City in 1993, 97 percent of clinical labs had found at least one strain of VRE. By 1994, 61 percent of hospitals nationwide had reported cases of VRE.

Vancomycin-Resistant SA (VRSA)—Prevention

In 1995, the Centers for Disease Control and Prevention (CDC) published recommendations for use of the antibiotic vancomycin in order to prevent the rapid spread of vancomycin resistance among bacteria. It emphasized the importance of wise use of vancomycin, continuing education for health care providers on prevention and control, and active screening and microbiological testing for resistant strains. The CDC recommends that vancomycin use be restricted to:

- Treatment of serious infections due to bacteria resistant to certain antibiotics such as methicillin.
- Treatment of serious infections due to bacteria in patients who have serious allergies to antibiotics such as methicillin.
- Treatment of antibiotic-associated colitis (an inflammation of the colon) that fails to respond to standard treatment or that is severe and life threatening.
- Prevention of endocarditis (an infection of heart tissue) following certain procedures in patients at high risk for endocarditis.
- Preventative surgical procedures involving implants at hospitals that have a high rate of infection due to methicillin-resistant *Staphylococcus aureus* (MRSA). In this case, treatment should be discontinued after a maximum of two doses.

Vancomycin-Resistant SA (VRSA)—Research (Promising Therapies)

Research continues along several lines to develop new therapies to cure infections that are caused by emerging *Staphylococcus aureus* bacteria that are resistant to the antibiotic vancomycin. (called VRSA). Some researchers hope to improve the effectiveness of vancomycin by modifying its structure. One promising experiment showed that a subpart of the vancomycin molecule killed bacteria 10 times better than the whole molecule. Other modifications to vancomycin may produce additional, effective antimicrobial drugs.

Another promising therapy uses synthetic peptides (short protein molecules) to block the release of toxins produced by *Staphylococcus aureus* (SA). One of the reasons that SA is so virulent is that it produces potent toxins. If the release of the toxins is prevented, much of the damage caused by SA is also prevented. The peptides bind to a receptor on the surface of the SA bacterium that controls the release of toxins. In preliminary tests, researchers have used synthetic peptides to reduce toxin release, curing mice infected with SA. Even though the peptides do not kill the bacteria, by preventing the damage caused by SA they could give patients' immune systems enough of an edge to knock out the infection. Research is needed to bring such a therapy to reality.

Other research studies may lead to the development of effective vaccines against SA or the toxins it produces. Scientists are currently testing yet another strategy. To slow the growth of virulent strains of SA, they infect patients with a non-disease-causing strain of SA. The hope is that the non-disease-causing strain will crowd out the virulent strain.

Vancomycin-Resistant SA (VRSA)—Risk Factors

People at the greatest risk from infections caused by emerging *Staphylococcus aureus* that are resistant to the antibiotic vancomycin (called VRSA) are the same as those at risk from the usual *Staphylococcus aureus* (SA) bacteria: people who have weak immune systems due to injury, illness, or age (either very young or very old). At particular risk will be hospital patients, because their health is already compromised and they are more likely to encounter VRSA in hospitals. Because of the increased risk, a VRSA epidemic might discourage people from having elective surgeries and make nonelective surgery more risky.

Vancomycin-Resistant SA (VRSA)—Vancomycin (Definition)

Vancomycin is a naturally occurring compound, derived from a fungus. It is also an antibiotic-of-last-resort: Vancomycin is the only drug effective against infections caused by strains of *Staphylococcus aureus* (SA) that are resistant to all of the other drugs that previously cured SA infections.

Scientists do not know precisely how vancomycin kills bacteria. They hypothesize that it interferes with cell wall formation. A bacterium without an intact cell wall is likely to rupture during growth and cell division; thus, any drug that prevents or disturbs cell wall formation will kill the bacterium.

Proposal Criteria Matrix

Read the script segments and use the databases to learn about the three infectious diseases addressed by the proposal. Make notes in the table below about the magnitude of each situation and the effectiveness of each plan.

Proposal Criteria Matrix

Proposal	Criteria	
	What Is the Magnitude of the Situation?*	How Effective Is the Plan?***
Proposal 1—AIDS Produce and distribute drugs to HIV-positive individuals.		
Proposal 2—Measles Produce and distribute vaccine to susceptible people.		
Proposal 3—VRSA Infections Develop new drug therapies against <i>Staphylococcus aureus</i> .		

***To determine magnitude, ask yourself questions such as the following:**

- How many people are affected by the disease? Who are they? Where are they?
- What are the consequences of having the disease, both for the affected individual and for society? How serious are the consequences?

****To determine effectiveness, ask yourself questions such as the following:**

- Is there a treatment for the disease? How effective is it? Are there any problems with the treatment?
- Are there preventive measures for the disease? How effective are they? Are there any problems with the preventive measures?
- Is there a way to get the treatment or preventive measures to those who are affected?
- What are the costs of the treatment or the preventive measures? What is the cost of delivering treatment or enforcing the preventive measures?
- If there is no treatment or prevention, is there a plan for developing an effective treatment or prevention that is likely to be successful?

Proposal Summary Matrix

Review the notes you made on the *Proposal Criteria Matrix*. Place checkmarks in the matrix below to indicate the magnitude and level of effectiveness of each of the three proposals. Use the following scale:

- ✓ = low magnitude/effectiveness
- ✓✓ = intermediate magnitude/effectiveness
- ✓✓✓ = high magnitude/effectiveness

Below the matrix, write the name of the proposal you recommend for funding and the reason for recommending that proposal instead of the others.

Proposal Summary Matrix

Proposal	Criteria	
	What Is the Magnitude of the Situation?	How Effective Is the Plan?
Proposal 1—AIDS		
Proposal 2—Measles		
Proposal 3—VRSA Infections		

Proposal recommended for funding:

Reasons for recommendation:

Reflection Questions

1. How did understanding the biology of infectious diseases help you make your decision?

2. What else did you consider in making your decision?